IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: David WALLACH et al

Application No.: 09/824,134 Conf. No. 2547

Filed: April 3, 2001

For: MODULATORS OF THE FUNCTION OF FAS/APO1 ...

Art Unit: 1642

Examiner: M. Davis

Washington, D.C.

Atty.'s Docket: WALLACH=16A

Date: December 6, 2004

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Sir:

Transmitted herewith is a [XX] Appeal Brief [ ] _____
in the above-identified application.

[ ] Small Entity Status: Applicant(s) claim small entity status. See 37 C.F.R. §1.27.

[ ] No additional fee is required.

[XX] The fee has been calculated as shown below:

	(Col. 1) CLAIMS REMAINING AFTER AMENDMENT		(Col. 2) HIGHEST NO. PREVIOUSLY PAID FOR	(Col. 3) PRESENT EXTRA EQUALS	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
TOTAL	* 9	MINUS	** 20	0	x 9	$		x 18	$
INDEP.	* 1	MINUS	*** 3	0	x 43	$		x 86	$
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+ 145	$		+ 290	$
					ADDITIONAL FEE TOTAL	$	OR	TOTAL	$

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.

** If the "Highest Number Previously Paid for" IN THIS SPACE is less than 20, write "20" in this space.

*** If the "Highest Number Previously Paid for" IN THIS SPACE is less than 3, write "3" in this space.

The "Highest Number Previously Paid For" (total or independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment of the number of claims originally filed.

[XX] Conditional Petition for Extension of Time
If any extension of time for a response is required, applicant requests that this be considered a petition therefor.

[XX] It is hereby petitioned for an extension of time in accordance with 37 CFR 1.136(a). The appropriate fee required by 37 CFR 1.17 is calculated as shown below:

Small Entity			Other Than Small Entity		
Response Filed Within			Response Filed Within		
[ ]	First	- $ 55.00	[ ]	First	- $ 110.00
[ ]	Second	- $ 215.00	[ ]	Second	- $ 430.00
[ ]	Third	- $ 490.00	[ ]	Third	- $ 980.00
[ ]	Fourth	- $ 765.00	[XX]	Fourth	- $ 1530.00
Month After Time Period Set			Month After Time Period Set		

[ ] Less fees ($_____) already paid for ___ month(s) extension of time on _____.

[ ] Please charge my Deposit Account No. 02-4035 in the amount of $_____.

[XX] Credit Card Payment Form, PTO-2038, is attached, authorizing payment in the amount of $ 1,530.00 _____.

[ ] A check in the amount of $_____ is attached (check no.).

[XX] The Commissioner is hereby authorized and requested to charge any additional fees which may be required in connection with this application or credit any overpayment to Deposit Account No. 02-4035. This authorization and request is not limited to payment of all fees associated with this communication, including any Extension of Time fee, not covered by check or specific authorization, but is also intended to include all fees for the presentation of extra claims under 37 CFR §1.16 and all patent processing fees under 37 CFR §1.17 throughout the prosecution of the case. This blanket authorization does not include patent issue fees under 37 CFR §1.18.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
DAVID **WALLACH**,
MARK BOLDIN, EUGENE VARFOLOMEEV, and
IGOR METT
Application No. 09/824,134
Filed: April 3, 2001

MODULATORS OF THE FUNCTION OF FAS/AP01 RECEPTORS

Examiner: Minh Tam B Davis
Art Unit: 1642

APPEAL BRIEF

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REAL PARTY IN INTEREST

The present application is owned by Yeda Research and Development Co. Ltd., which is the research and development arm of the Weizmann Institute of Science in Rehovot, Israel. The exclusive licensee of the present invention is Inter-Lab Limited, an Israeli company of Ness-Ziona, Israel. Inter-Lab Limited is a subsidiary of InterPharm Laboratories Limited, an Israeli company of Ness-Ziona, Israel, which is a member of the Serono group of companies, whose parent company is Serono S.A., a holding company under which there are many subsidiaries worldwide.

RELATED APPEALS AND INTERFERENCES

The present application is a continuation of application 08/860,082 filed August 19, 1997. On March 10, 2002, the examiner suspended proceedings in said parent application "due to a potential interference". Subsequently, prosecution was reopened to issue a new rejection of some of the claims. An amendment has recently been filed deleting the rejected claims without prejudice toward the continuation of prosecution thereof in a continuing application, so that the only claims remaining in the case are claims that have been deemed allowable. It is not known if there is still a potential interference with respect to the remaining allowable claims.

Aside from the above, there are no related appeals or interferences.

STATUS OF CLAIMS

Claims 1-7, 11 and 14 are pending in the present application and are subject to the present appeal. Claims 8-10, 12 and 13 have been cancelled.

STATUS OF AMENDMENTS

No amendment has been made subsequent to the final rejection of March 4, 2004, in this case.

SUMMARY OF CLAIMED SUBJECT MATTER

The only independent claim in this case is claim 1. No means plus function or step plus function as permitted by 35 U.S.C. §112, sixth paragraph, are present in claim 1.

Claim 1 is directed to an isolated DNA molecule as defined by any one of three alternative numbered paragraphs. Paragraph (1) of claim 1 is directed to the isolated DNA molecule comprising a DNA sequence that encodes the MORT-1 protein, having the amino acid sequence of SEQ ID NO:2. Thus, this portion of the claim is directed to any isolated DNA molecule that includes within it any DNA sequence that encodes the amino acid sequence of SEQ ID NO:2. The amino acid sequence of SEQ ID NO:2 is shown in Fig. 4. The protein having the amino acid sequence of SEQ ID NO:2 is defined in the specification as HF1 (see line 3 of the amended paragraph beginning at page 14, line 20, of the present specification). This novel protein is also known as MORT-1 (for "Mediator Of Receptor Toxicity"). See page 7, lines 19-20.

This paragraph of claim 1 covers not only the DNA sequence of the natural cDNA that encodes MORT-1, but also those sequences that are degenerate as a result of the genetic code to the cDNA sequence derived from the coding region of the native MORT-1 protein (see page 8, line 13-14). The claimed DNA sequence in paragraph 1 may be longer than the

sequence that encodes the MORT-1 protein so as to encompass, for example, vectors that contain the DNA sequence of the invention, but which also contain additional DNA regions that allow them to be capable of being expressed in suitable eukaryotic or prokaryotic host cells (see page 8, lines 24-27). Note that the sentence bridging pages 16 and 17 indicates that the MORT-1 protein may be conjugated to another molecule, for example an antibody, enzyme, receptor, etc., as are well known in the art. Note also the first paragraph on page 30, which refers to recombinant animal virus vectors encoding the MORT-1 protein, but which also encode a virus surface protein.

In paragraph (2) of claim 1, there is claimed an isolated DNA molecule comprising a DNA sequence that encodes an analog of the MORT-1 protein having the amino acid sequence of SEQ ID NO:2. This analog must bind with the intracellular domain of the FAS ligand receptor (FAS-IC). Furthermore, the DNA sequence which encodes that analog must be capable of hybridizing to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions. See page 8, lines 10-12. Note that while the isolated DNA molecule "comprises" the DNA sequence that encodes the analog of the MORT-1 protein, it is only the DNA sequence which encodes the analog that must be capable of

hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions.

The specification teaches that such analogs may be prepared by standard procedures, citing Sambrook et al, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (1989). See page 16, lines 5-6, and page 47, lines 1-2. In such procedures, the DNA sequences encoding the MORT-1 protein have one or more codons deleted, added or substituted by another to yield analogs having at least a one amino acid residue change with respect to the native protein (see page 16, lines 7-9). Acceptable analogs are those that retain at least the capability of binding to the intracellular domain of the FAS-R (see page 16, lines 9-10).

In paragraph (3) of claim 1, there is claimed an isolated DNA molecule comprising a DNA coding sequence consisting of a DNA sequence that encodes a fragment of the MORT-1 protein that binds with FAS-IC. The MORT-1 protein is that of the amino acid sequence of SEQ ID NO:2. See page 16, lines 20-28 of the present specification. Note that while the isolated DNA molecule "comprises" the DNA sequence that encodes a fragment of the MORT-1 protein, it is only the DNA sequence that encodes the fragment that must be capable of binding with FAS-IC.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

In the final rejection of March 4, 2004, the sole rejection in the case was the rejection of claims 1-7, 11 and 14 under 35 U.S.C. §112, first paragraph, for lack of enablement for a DNA sequence encoding an analog of the MORT-1 protein (SEQ ID NO:2) for the reasons of record in paper no. 10. While the enablement rejection in paper no. 10 contained several different reasons why the examiner considered that the claims did not comply with this section of 35 U.S.C. §112, the only one of applicants' arguments set forth in the amendment of December 3, 2003, which the examiner did not deem to be persuasive, was the one relating to the interpretation of paragraph 2 of claim 1. Accordingly, it is applicants' understanding that the portion of the rejection relating to the interpretation of claim 1(2) is the only part of the rejection that remains subject to this appeal.

In paper no. 10, in the part of the rejection in section 3 of the rejection, beginning at page 9, the examiner stated:

> If applicant could overcome the above 112, first paragraph, claims 1-7, 11 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling [sic] a cDNA sequence of SEQ ID NO:1, does not reasonably provide enablement for an analog of a DNA sequence encoding the amino acid sequence of SEQ ID NO:2, which binds to the intracellular domain of the FAS ligand receptor (FAS-IC),

and is capable of "hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-7, 11 are drawn to a DNA sequence encoding the amino acid sequence of SEQ ID NO:2, or an analog thereof, which binds to the intracellular domain of the FAS ligand receptor (FAS-IC), and is capable of "hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions", or a fragment thereof, which binds to FAS-IC, a vector comprising said DNA sequence, host cells transformed with said vector, and a method for producing polypeptide which binds to FAS-IC, using said host cells.

Claims 1-7, 11 encompass unrelated sequences with unknown function encoding a polypeptide that shares with SEQ ID NO:2 a fragment that binds to FAS-IC.

Applicant has not enabled these types of modified DNAs in the specification.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Such unpredictability would equally apply to DNA sequences which encode proteins. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. Journal of Cell Biology, 1990, 11:2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988,

> 8:1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8):2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1):47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.
>
> Further, the claims encompass polynucleotides comprising non-disclosed nucleic acid sequences attached to polynucleotides under moderately stringent conditions. When given the broadest possible interpretation, it would be expected that a substantial number of the hybridizing molecules encompassed by the claims **would not** share either structural or functional properties with polynucleotides that encode MORT-1 protein.
>
> In view of the above, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed. [Emphasis Original]

In the final rejection of March 4, 2004, the examiner responded to applicants' arguments as follows:

> Applicant argues as follows:
>
> The examiner's interpretation of claim 1(2) is incorrect where the examiner states that a substantial number of the hybridizing molecules encompassed by the claims that encode MORT-1 protein. The DNA sequence of claim 1(2) must encode an analog, which analog binds with the FAS-IC, and it is that sequence which must be capable of

hybridizing to the CDNA encoding SEQ ID NO:2 under moderately stringent conditions. Thus, is not some other part of the DNA molecule that may hybridize to the CDNA encoding SEQ ID NO:2, but must be that sequence which encodes the analog that binds with FAS-IC. If that that [sic] sequence both binds to FAS-IC and hybridizes to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions, then it would be expected to share substantial sequence identity with SEQ ID NO:2. As explained in previous amendment, of February 24, 2003, it would be expected to require at least 75% homology. Any such sequence thus shares structural and functional (or physical) properties with polynucleotides that encode MORT-1 protein.

Applicants arguments set forth in paper of 12/03/03 have been considered but are not deemed to be persuasive for the following reasons:

The claims encompass variants, with unknown structure and function, wherein said variants share with the claimed polynucleotide sequence a polynucleotide fragment that encodes a fragment of SEQ ID NO:2 that binds to FAS-IC, and wherein said variants hybridize to the claimed polynucleotide via said polynucleotide fragment under moderately stringent conditions.

Applicant has not taught how to make said variants such that they would have the function and properties of the claimed polynucleotide encoding SEQ ID NO:2.

One would not know how to make the claimed variants in view of a lack of adequate teaching in the specification, and in view of the unpredictability of protein chemistry, as taught by Burgess et al, Lazarus et al, Tao et al and Gillies et al, all of record, and in view that said

unpredictability applies as well to DNA sequences which encode proteins.

ARGUMENT

Determining Which Analogs Bind FAS-IC Would Not Entail Undue Experimentation

The sole rejection remaining in the final rejection of March 4, 2004, relates to enablement for paragraph 2 of claim 1. The examiner states that applicants have not taught how to make variants that are capable of hybridizing to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions, such that those variants would bind with the intracellular domain of the FAS ligand receptor (FAS-IC). The examiner states that one would not know how to make the claimed variants in view of a lack of adequate teaching in the specification, and in view of the unpredictability of protein chemistry and the DNA sequences that encode proteins.

The examiner's argument fails in view of the fact that it is not necessary to know in advance which variants of the cDNA encoding SEQ ID NO:2 would bind with FAS-IC. It is not necessary to decide whether protein chemistry is predictable or unpredictable. The point is that mutations in the cDNA can be randomly made with all of the random mutations being tested *en masse* for hybridization under moderately stringent conditions. All those that hybridize can then be cloned so as to produce an expression product of the DNA in question, and that expression product tested by a very simple binding assay to determine if it binds to the intracellular

domain of FAS (FAS-IC). Whatever is found to hybridize under moderately stringent conditions and to encode a polypeptide that binds to the FAS-IC falls within the scope of the claim. Anything else does not. None of these steps involve undue experimentation.

The specification at page 16 cites Sambrook et al (1989) for standard procedures to prepare analogs. Among such standard procedures are treatment of double-stranded DNA with chemical mutagens, treatment of single-stranded DNA with sodium bisulfite, and treatment of single-stranded DNA with chemicals that damage all four bases, which appear at pages 15.105-15.107 of the Sambrook reference. These are all procedures that would have been well known to those of ordinary skill in the art at the time of the effective filing date of the present application. Simple *in vitro* binding assays are described, for example, at page 34, lines 3-13, of the specification.

The amount of experimentation that may be permitted in order to satisfy the enablement requirement of 35 U.S.C. §112 is discussed in *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In this regard, *Wands* states, 858 F.2d at 736-737, 8 USPQ2d at 1404:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

> experimentation. "The key word is 'undue,' not 'experimentation.'"
>
> > The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 878-879; 169 USPQ 759, 762-763 (2d Cir. 1971), *cert. denied,* 404 U.S. 1018, 30 L. Ed. 2d 666, 92 S. Ct 680 (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed***. [Footnotes omitted - the latter quote being from *In re Jackson,* 217 USPQ 804, 807 (Bd. App. 1982)]

Wands goes on to state, 858 F.2d at 737, 8 USPQ2d at 1404:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. [Footnotes omitted]

In analyzing these factors in this case, the conclusion must be reached that the experimentation is not

undue. As to the first factor, the quantity of experimentation may be significant, as random mutations would have to be generated, hybridization experiments conducted, and screening conducted of those that are found to hybridize under moderately stringent conditions using a simple binding assay. However, in the *Wands* case, it was found that routine screening does not necessarily amount to undue experimentation.

With respect to the second factor, the amount of guidance or direction presented, the specification refers to the Sambrook reference, which is the laboratory manual used by everyone of ordinary skill in this art. Everything in it is known and within the skill of those of ordinary skill in the art. Less guidance is needed for well-known techniques. Substantial guidance as to a specific binding screen is provided at page 34.

As to the third factor, the presence or absence of working examples, the binding assay at page 34 is sufficiently detailed to serve as a working example.

As to the fourth factor, the nature of the invention, the nature of the invention is such that substantial experimentation is acceptable. As will be discussed in the following factors, the field of this invention requires a very high level of skill in the art, and

practitioners are well inured to screening that takes substantial experimentation quantitatively.

As to the fifth factor, the state of the prior art, moderate stringency hybridization, random mutagenesis and binding assays are all well-documented in the prior art. The examiner has not doubted this fact, and so it has not been necessary to submit evidence proving it. The present invention does not involve any of these specific techniques *per se*. Their use on the novel DNA sequence of the present invention is the advance made by the present inventors.

As to the sixth factor, the relative skill of those in the art, those of ordinary skill in the art of recombinant DNA technology is very high, usually requiring a Ph.D. and/or substantial laboratory experience. For such persons, a greater amount of experimentation would be considered to be routine than for technologies requiring a lower level of skill in the art.

As to the seventh factor, the predictability of the art, predictability is not relevant here, as no predictability is necessary. One need only do the experiments and screen; the results will provide all of the answers. It is not necessary to predict the answers in advance.

As to the eighth factor, the breadth of the claims, paragraph 2 of claim 1 is not so broad so as to require undue

experimentation to find what would fall within it for the reasons as discussed above with respect to all of the other factors.

Accordingly, as in *In re Wands*, analysis of the facts of the present case, considering the factors enumerated in *Ex parte Forman*, leads to the conclusion that undue experimentation would not be required to practice the invention. There was a high level of skill in the art at the time when the application was filed and all of the methods needed to practice the invention were well known. Accordingly, reversal of the examiner and withdrawal of this rejection for all the claims now present in the case is respectfully urged.

CONCLUSION

The claims as submitted are believed to truly set forth the inventive concept of the present invention and to fully comply with the enablement requirement of the first paragraph of 35 U.S.C. §112. Accordingly, reversal of the examiner and allowance of claims 1-7, 11 and 14 are earnestly solicited.

Respectfully submitted,

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CLAIMS APPENDIX

This listing of claims includes all of the claims involved in the appeal.

Listing of Claims:

1. An isolated DNA molecule comprising:

(1) a DNA sequence which encodes the MORT-1 protein, having the amino acid sequence of SEQ ID NO:2;

(2) a DNA sequence which encodes an analog of said MORT-1 protein, which analog binds with the intracellular domain of the FAS ligand receptor (FAS-IC), which DNA sequence is capable of hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions; or

(3) a DNA coding sequence consisting of a DNA sequence which encodes a fragment of said MORT-1 protein which binds with FAS-IC.

2. An isolated DNA molecule in accordance with claim 1, comprising a DNA sequence encoding an analog of said MORT-1 protein which binds with FAS-IC, which DNA sequence is capable of hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions.

3. A vector comprising a DNA sequence according to claim 1.

4. A vector according to claim 3 which is capable of being expressed in a eukaryotic host cell.

5. A vector according to claim 3 which is capable of being expressed in a prokaryotic host cell.

6. Isolated transformed eukaryotic or prokaryotic host cells containing a vector according to claim 3.

7. A method for producing a polypeptide which binds to the intracellular domain of the FAS-R, comprising growing the isolated transformed host cells according to claim 6 under conditions suitable for the expression of an expression product from said cells, effecting post-translational modifications of said expression product as necessary for obtention of said polypeptide, and isolating said expressed polypeptide.

8-10 (Cancelled).

11. A recombinant animal virus vector encoding a virus surface protein capable of binding a specific target cell surface receptor and further including the sequence of a DNA molecule of claim 1.

12-13 (Cancelled).

14. An isolated DNA molecule in accordance with claim 1 wherein the entire said DNA sequence is a coding sequence encoding said polypeptide.

EVIDENCE APPENDIX

NONE

RELATED PROCEEDINGS APPENDIX

NONE